Notice of Allowability	Application No.	Applicant(s)	
	10/630,074	MILICH ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *8/9/006*.

2. ☒ The allowed claim(s) is/are *56-70, 72-102 and 104-124*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☒ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

1. Applicant's amendment filed on August 9, 2006, in response to the Final Office Action dated on June 13, 2006, is acknowledged. Claims 1-55, 71, and 103 were cancelled. Claims 56, 69, 90, and 102 were amended, new claims 117-124 were added.

2. Accordingly, Claims 56-70, 72-102 and 104-124 are pending.

EXAMINER'S AMENDMENT

3. An examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

4. Authorization for this Examiner's Amendment was given in a telephone interview with Applicant's representative Christine Lekutis on August 22, 2006.

5. Amend following claims:

56. A method of making a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

~~determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid is greater than or equal to 7.0, and adding~~ altering nucleotides ~~that encode an acidic amino acid to said~~ of said first nucleic acid to reduce said isoelectric point of said heterologous antigen below 7.0;

combining said first and second nucleic acids, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable ~~within said~~ within an immunodominant loop or ~~said~~ within an alpha-helix adjacent to said immunodominant loop; and

expressing said first and second nucleic acids to produce a modified hepadnavirus core antigen comprising the amino acids encoded by said first and second nucleic acids.

57. The method of Claim 56, wherein in the absence of said ~~adding~~ altering nucleotides, expression of said modified hepadnavirus core antigen yields 25 fold or less particles than does expression of a wild type hepadnavirus core antigen.

58. The method of Claim 56, wherein after ~~adding~~ said altering nucleotides ~~to said first nucleic acid~~, said heterologous antigen encoded by said first nucleic acid is determined to have an isoelectric point in the range of 3.0 - 5.0.

59. The method of Claim 56, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in a substitution of a non-acidic amino acid residue within said heterologous antigen, ~~with said~~ with an acidic amino acid residue.

61. The method of Claim 56, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in an insertion of ~~said~~ at least one acidic amino acid residue.

62. The method of Claim 61, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid ~~that flanks~~ residue flanks one side of said heterologous antigen.

63. The method of ~~Claim 62~~ Claim 61, wherein said at least one acidic amino acid residue ~~is a linker that flanks~~ flank both sides of said heterologous antigen.

69. A method of making a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

~~determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid is greater than or equal to 7.0, and adding~~ altering nucleotides ~~that encode an acidic amino acid to said~~ of said second nucleic acid at a position encoding a residue within an

immunodominant loop of said hepadnavirus core antigen or within an alpha-helix adjacent to said immunodominant loop;

combining said first and second nucleic acids, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable within said immunodominant loop or said alpha-helix adjacent to said immunodominant loop; and

expressing said first and second nucleic acids to produce a modified hepadnavirus core antigen comprising the amino acids encoded by said first and second nucleic acids.

70. (currently amended) The method of Claim 69, wherein in the absence of said ~~adding~~ altering nucleotides, expression of said modified hepadnavirus core antigen yields 25 fold or less particles than does expression of a wild type hepadnavirus core antigen.

74. The method of Claim 69, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in a substitution of a non-acidic amino acid residue within said hepadnavirus core antigen, ~~with said~~ with an acidic amino acid residue.

76. The method of Claim 69, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in an insertion of ~~said~~ at least one acidic amino acid residue.

77. The method of Claim 76, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid residue is within said immunodominant loop of said hepadnavirus core antigen.

78. The method of Claim 76, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid residue is within said alpha helix adjacent to said immunodominant loop.

79. The method of Claim 76, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid ~~that flanks~~ residue flanks one side of said heterologous antigen.

80. The method of ~~Claim 79~~ Claim 76, wherein said at least one acidic amino acid residue ~~is a linker that flanks~~ flank both sides of said heterologous antigen.

90. A method of making a nucleic acid that encodes a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus

core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

~~determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid is greater than or equal to 7.0, and adding~~ altering nucleotides ~~that encode an acidic amino acid to said~~ of said first nucleic acid to reduce said isoelectric point of said heterologous antigen below 7.0; and

combining said first and second nucleic acids so as to produce said nucleic acid that encodes said modified hepadnavirus core antigen, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable ~~within said~~ within an immunodominant loop or ~~said~~ within an alpha-helix adjacent to said immunodominant loop.

91. The method of Claim 90, wherein after ~~adding~~ said altering nucleotides, said heterologous antigen is determined to have an isoelectric point in the range of 3.0 - 5.0.

92. The method of Claim 90, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in a substitution of a non-acidic amino acid residue within said heterologous antigen, ~~with said~~ with an acidic amino acid residue.

94. The method of Claim 90, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in an insertion of ~~said~~ at least one acidic amino acid residue.

95. The method of Claim 94, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid ~~that flanks~~ residue flanks one side of said heterologous antigen.

96. The method of ~~Claim 95~~ Claim 94, wherein said at least one acidic amino acid residue ~~is a linker that flanks~~ flank both sides of said heterologous antigen.

102. A method of making a nucleic acid that encodes a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

~~determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid is greater than or equal to 7.0, and adding~~ altering nucleotides ~~that encode an acidic amino acid to said~~ of said second nucleic acid at a position encoding a residue within an immunodominant loop of said hepadnavirus core antigen or within an alpha-helix adjacent to said immunodominant loop; and

combining said first and second nucleic acids so as to produce said nucleic acid that encodes said modified hepadnavirus core antigen, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable within said immunodominant loop or said alpha-helix adjacent to said immunodominant loop.

106. The method of Claim 102, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in a substitution of a non-acidic amino acid residue within said hepadnavirus core antigen, ~~with said~~ with an acidic amino acid residue.

108. The method of Claim 102, wherein said ~~adding~~ altering nucleotides ~~that encode an acidic amino acid~~ results in an insertion of ~~said~~ at least one acidic amino acid residue.

109. The method of Claim 108, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid residue is within said immunodominant loop of said hepadnavirus core antigen.

110. The method of Claim 108, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid residue is within said alpha helix adjacent to said immunodominant loop.

111. The method of Claim 108, wherein said ~~adding nucleotides that encode an acidic amino acid results in~~ at least one acidic amino acid ~~that flanks~~ residue flanks one side of said heterologous antigen.

112. The method of ~~Claim 111~~ Claim 108, wherein said at least one acidic amino acid residue ~~is a linker that flanks~~ flank both sides of said heterologous antigen.

118. The method of Claim 56, wherein said heterologous antigen is ~~less than~~ 20 or fewer amino acids in length.

6. The following is an examiner's statement of reasons for allowance:

(1) The rejection of claims 56-116 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to the claims.

(2) The rejection of claims 56-116 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement is withdrawn in view of the amendment to the claims.

(3) Rejection of claims 56-66, 68-83, 85-99 and 101-115 under 35 U. S. C. 102(b) is withdrawn in view of the amendment to the claims and Applicant's argument.

(4) Rejection of claims 56-116 under 35 U. S. C. 103(a) is withdrawn in view of the amendment to the claims and Applicant's argument.

(5) The rejection of claims 56-116 under the nonstatutory double patenting over claims

25-30 of copending Application No. 10/630,070 is withdrawn in view of the cancellation of claims 25-30 of copending Application No. 10/630,070

7. The instant invention is directed to a method of making a modified hepadnavirus core antigen comprising foreign antigens by altering a foreign antigen so that the isoelectric point of the antigen is blow 7.0 and incorporating the foreign antigen into said core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen (WHcAg), a ground squirrel hepadnavirus core antigen (GSHcAg) and a human hepadnavirus core antigen (HBcAg).

8. One of the closest prior arts cited in the application is Birkett's (US 6,231,864). Birkett teaches a strategically modified hepatitis B core protein to include a T cell epitope. Birkett teaches the sequence similarity between HBcAg and WHcAg. However, Birkett does not teach or suggest modifying amino acid residues of antigen so that the inserting heterologous antigen has a pI below 7.0.

9. Other art cited in the application includes Pumpens. Pumpens teaches the utility of human hepatitis B virus core antigen particles as epitope carriers. Pumpens teaches that human hepatitis B virus core antigen shows strong conservation with hepatitis core antigen sequences from other species, including WHV, GSHV (See page 64, col. 2), but does not teach and suggest a method of making a modified core antigen from other species as a carrier, including WHcAg and GSHcAg, as claimed by instant application. The reference also does not teach inserting a heterologous antigen that has a pI below 7.0

10. The Examiner is not aware of any suggestion in the prior art of the record that teaches and suggests a method of making a modified hepadnavirus core antigen by altering a foreign antigen so that the isoelectric point of the antigen is blow 7.0 and incorporating the foreign antigen into said core antigen, nor use of WHsAg and GSHcAg as a carrier,

11. Accordingly, claims 56-124 are allowed.

12. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bo Peng, Ph.D.
8/25/06

MARY E. MOSHER, PH.D.
PRIMARY EXAMINER